Antibiotic Resistance

DQTC Bulletin

Drug Quality and Therapeutics Committee

Antibiotic Review and Ontario Drug Benefit Formulary Listing Changes

Ontario

February 2001

Executive Summary

Rising rates of antimicrobial resistance have evolved into a significant public health problem on a global basis. The morbidity, mortality and financial costs of multiple drug resistant infections for which there are few or no effective therapies pose an increasing burden for health care systems.

In Canada, the most important strains of resistant bacteria are penicillin-resistant *Streptococcus pneumoniae* (PRSP), methicillin-resistant *Staphylococccus aureus* (MRSA), and vancomycin-resistant enterococci (VRE). At the same time, available evidence suggests that 51% of antibiotics in Canada are being prescribed for patients with upper respiratory tract infections, the common cold and other viral infections for which antibiotics are not indicated.

While solutions to the problem of antimicrobial resistance are complex and multifactorial, the wise and judicious use of antibiotics must form an integral part of any effort aimed at decreasing, and possibly reversing, the emergence and spread of resistance.

In light of these concerns, in 1999, the Ontario Ministry of Health and Long-Term Care (MOHLTC) initiated a comprehensive review of all antibiotics listed in the Ontario Drug Benefit Formulary/Comparative Drug Index (Formulary). The purpose of the review was to assess the increasing threat of antimicrobial resistance and to ensure that all antibiotics listed in the Formulary were being used appropriately in accordance with current clinical evidence.

The review was conducted by an 11–member multidisciplinary Subcommittee of the Drug Quality and Therapeutics Committee (DQTC) – the Ministry's expert drug advisory committee. Manufacturers were given two opportunities to submit information on their products: once at the beginning of the review process, and later following the Subcommittee's preliminary recommendations. Prior to making final recommendations, the Subcommittee carefully considered each of the manufacturers' responses to the proposed changes. Following a review of the Subcommittee's report, the DQTC made their final recommendations to the MOHLTC. The MOHLTC has accepted the recommendations of the DQTC. Accordingly, several changes have been made to antibiotic listings in the Formulary. The listing changes and the rationale for the changes are outlined in the document that follows.

The most significant listing changes affect the quinolone antibiotics, some of which were formerly listed as General Benefit products. Ciprofloxacin, levofloxacin and ofloxacin will now be listed as Limited Use products; norfloxacin will remain a General Benefit product. The Subcommittee was particularly concerned about increasing rates of resistance to this class of antibiotics and the spread of cross-resistance from older to newer quinolones. Thus, the listings for ciprofloxacin, levofloxacin and ofloxacin have been revised to encourage the most appropriate use of these agents and to limit the spread of resistance.

Three agents – clarithromycin, azithromycin and amoxicillin/clavulanic acid – will remain as General Benefit products on a conditional basis; their respective usage and resistance patterns have been flagged by the Subcommittee for reassessment in one year's time. These conditional listings reflect the Subcommittee's concerns that, with the new restrictions on the use of quinolones, a potential increase in macrolide use may result in significant resistance developing to these agents.

Some rarely used products have been delisted.

Introduction

In recent years, rapidly increasing rates of antimicrobial resistance have evolved into a significant global clinical and public health problem. The morbidity, mortality and financial costs of multiple drug resistant infections for which there are no effective therapies pose an increasing burden for health care systems worldwide and Canada is no exception.[1,2] Without effective public health strategies, grim warnings of a post-antibiotic era may become a reality.[2,3] A number of factors have played, and continue to play, a role in this dilemma. However, chief among them is the overuse of antibiotics – a factor that has been directly correlated with increasing resistance.

In Canada, concerns have focused primarily on antibacterial resistance to common causes of community-acquired infectious diseases, such as pneumonia, and selected hospital-acquired infections. Currently, the most important strains of resistant bacteria are penicillin-resistant *Streptococcus pneumoniae* (PRSP), methicillin-resistant *Staphylococccus aureus* (MRSA), and vancomycin-resistant enterococci (VRE).[4] In Canadian hospitals, there has been a rapid emergence of resistance to both Gram-positive and Gram-negative organisms. Rates of MRSA in hospitalized patients in Ontario have increased dramatically over the past 3 years.[5–8] While VRE has only recently been introduced to Canadian hospitals, within the span of 11 years it has become endemic in U.S. hospitals.[9] The high frequency of use of antibiotics in the hospital setting is thought to be responsible for the increasing rates of *Clostridium difficile* – associated diarrhea in developed countries, such that it is now the predominant, if not the only, cause of infectious diarrhea in hospitalized patients.[10] At this time, other causes of community-acquired infection such as *H. influenzae* are of less concern. While approximately 30% of *H. influenzae* are beta-lactamase producing, the activity of most beta-lactams has not been adversely affected.[11, 12] In addition, agents such as the fluoroquinolones remain highly active against *H. influenzae*.[12]

The emergence of antimicrobial resistance is viewed by Health Canada as a major health care issue both in the community and hospital settings.[4,13] However, the issue of resistance is both complex and multifactorial. To deal with the complexities, a multifaceted approach on both a collective and individual basis is considered the optimal approach. Both federally and provincially (including Ontario), a number of collaborative initiatives with the medical community and public health are underway to combat the development and transmission of antimicrobial resistant organisms.[14–17]

As indicated in the cover letter, a number of initiatives are currently underway in Ontario across the government to address this serious public health issue. In concert with the Drug Programs Branch initiatives, the Public Health Branch will be continuing its initiatives regarding antibiotic resitance.

The wise and judicious use of antibiotics must form an integral part of any effort aimed at decreasing, and possibly reversing, the spread of resistance. Importantly, several studies have shown that, where communities and countries have adopted policies to decrease antibiotic use, resistance has decreased.[13,18–20]

In Canada, annual expenditures for antibiotics exceed $485 million; the Ontario Drug Benefit Program alone spent approximately $50 million in 1999 on antibiotics.[21] One major contributor to these high costs is the suboptimal use of antibiotics. Extrapolating from recent Canadian data on prescribing in preschool children, 51%

Antibiotic Review Process

of antibiotics are being prescribed for upper respiratory tract infections, the common cold and other viral infections for which antibiotics are ineffective.[22] This data is consistent with estimates by the Centers for Disease Control and Prevention that as much as half of all antibiotic prescriptions are unnecessary.[23] In addition, it is thought that significant costs are being incurred through the excessive use of expensive broad-spectrum agents.[21]

Antibiotic Review Process

In light of these concerns, in 1999, the Ontario Ministry of Health and Long-Term Care (MOHLTC) initiated a comprehensive review of all antibiotics listed in the Ontario Drug Benefit Formulary/Comparative Drug Index (Formulary). This review of the Formulary antibiotic listings was conducted in concert with initiatives undertaken by the Ministry's Public Health Branch (e.g. SPARO – Strategic Planning for Antibiotic Resistance in Ontario).[24] Similar reviews have recently been completed or are ongoing in a number of other Canadian provinces. In addition, several other jurisdictions are actively addressing the issue of antibiotic resistance across Canada.[17]

The Ministry's expert drug advisory committee, the Drug Quality and Therapeutics Committee (DQTC), was asked to conduct the antibiotic review. The purpose of the review was to assess the increasing threat of resistance and to ensure that all antibiotics listed in the Formulary were being used appropriately in accordance with current clinical evidence.

An Antibiotic Review Subcommittee of the DQTC was formed to undertake the review; meetings of the Subcommittee were held from the Fall of 1999 to the Spring of 2000. The 11–member Subcommittee represented a broad cross section of Ontario health care practitioners. Members were selected on the basis of their practice experience, the geography of their practice, and their professional affiliations. The Subcommittee included experts in the fields of infectious disease, respirology, pediatrics, geriatrics, family medicine, internal medicine, emergency medicine and pharmacy. The Subcommittee also drew on the experiences of other provincial antibiotic review committees. An observer from the Ontario Public Health Branch attended the Subcommittee meetings.

Each antibiotic listed in the Formulary was reviewed; in total, over 50 agents were evaluated. This review did not extend to other types of antimicrobial agents such as the antifungals, antiprotozoals and antivirals. Guiding principles of the review are outlined in the paragraph below. Manufacturers were offered an opportunity to submit information pertaining to their products at the beginning of the review process. The Subcommittee made preliminary recommendations that were subsequently considered by the DQTC as a whole. Manufacturers were then offered an opportunity to comment on the preliminary recommendations. The Antibiotic Review Subcommittee considered each of the manufacturers' responses before finalizing their recom-

Principles of the Review

mendations. Following a thorough review of the Subcommittee's report, the DQTC then made their final recommendations to the Ministry. The Ontario Ministry of Health and Long-Term Care has accepted the recommendations of the DQTC. Accordingly, several changes have been made to antibiotic listings in the Formulary.

Principles of the Review

In keeping with the goals set for the antibiotic review, two overriding principles taken in concert guided the deliberations of the Subcommittee. The first principle was to review patterns of usage of antibiotics listed in the Formulary with respect to their propensity to result in increased resistance. Published reports of antibiotic resistance patterns in Ontario and Canada were reviewed. Where there was considerable evidence of increased antibiotic use and the presence of an increase in resistant organisms, the Subcommittee considered recommendations to change the Formulary listing. In cases where resistance rates were currently stable or low but have the potential to rise, the Subcommittee recommended that the agent retain its current listing for a period of one year, after which its status would be reassessed.

The second principle of this review was to harmonize the Formulary listings of antibiotics with current clinical evidence. Where there was evidence of significant antibiotic usage that was inconsistent with clinical evidence, the Subcommittee considered recommendations to change the Formulary listing. In addition, in some cases, where there was evidence of better value from suitable alternative agents, the Subcommittee considered recommendations to alter the Formulary listing.

Changes to the Ontario Drug Benefit Formulary/Comparative Drug Index

A detailed summary of the listing status for all antibiotics is outlined in the table at the end of this document (Appendix A); major changes are outlined in the table below, followed by an overview of the rationale upon which each change was based. The most significant listing changes affect the quinolone antibiotics, some of which were formerly listed as General Benefit products, but will now be listed as Limited Use products. Three other agents – two newer macrolides and one penicillin combination – will remain as General Benefit products on a conditional basis; their respective usage and resistance patterns have been flagged by the Antibiotic Review Subcommittee for reassessment in one year's time. Some products have been delisted either because the product has been discontinued or because relatively few claims have been made; in other cases, more effective and better value alternatives are available.

Rationale for Listing Changes

Major Listing Changes

Antibiotic Class	Antibiotic Agent	Listing Status
Quinolones	Ciprofloxacin Levofloxacin Ofloxacin	Limited Use products.
	Norfloxacin	General Benefit product.
Macrolides	Clarithromycin Azithromycin	Continue to be listed as General Benefit products. Listing status will be reassessed in 1 year.
Penicillins	Amoxicillin/ Clavulanic Acid	Continue to be listed as a General Benefit product. Listing status will be reassessed in 1 year

Rationale for Listing Changes

Quinolones

The Antibiotic Subcommittee was particularly concerned about increasing rates of resistance to this class of antibiotics as well as the spread of cross-resistance from older to newer quinolones. Since 1993/1994, there has been a significant increase in the prevalence of fluoroquinolone-resistant strains of *Streptococcus pneumoniae*, especially in those 65 years of age and older, and in those living in Ontario compared with the rest of Canada.[25] This emergence of *S. pneumoniae* resistance has been empirically linked with the increased use of fluoroquinolones[25]; in Ontario, the usage of fluoroquinolones has increased 750% since 1988. In addition to fluoroquinolone-resistant *S. pneumoniae*, community–acquired quinolone resistance has also been reported in Enterobacteraciae isolates, *Campylobacter jejuni* and *Neisseria gonorrhoea*.

The Subcommittee also noted that, in general, the fluoroquinolones should be used as second line agents; however, they are often used as first line agents in a community context, even where gram-positive pathogens are expected to predominate. It was further noted that the use of quinolones for acute exacerbations of chronic bronchitis should be limited only to those patients with risk factors. Extensive use of this class of drugs has represented a significant cost to the ODB Formulary (40% of total antibiotic expenditures). At the same time, the Subcommittee recognized that the high bioavailability and broad spectrum of ciprofloxacin, levofloxacin and ofloxacin render them highly

Rationale for Listing Changes (continued)

suitable for step-down therapy from parenteral therapy for a number of indications.

Ciprofloxacin: Ciprofloxacin had been listed in the Formulary as a General Benefit product. The rationale for restricting the use of ciprofloxacin was based on reports of rising rates of resistance to this agent and others in its class, as well as evidence of inappropriate usage in settings where suitable alternatives are available. The Subcommittee noted that, through communication with other Ministries, there has been no evidence of any deleterious effects in the overall health of patients in those Canadian provinces that have already restricted the use of iprofloxacin.

In addition to the fluoroquinolone class data mentioned above, large institutional studies have demonstrated significant increases in resistance rates of Acinetobacter species and *Pseudomonas aeruginosa* specifically to ciprofloxacin. The Public Health Laboratory of Ontario has demonstrated a high level (49%) of methicillin-resistant *Staphylococccus aureus* (MRSA) resistance to ciprofloxacin; rates exceeding 80% have been reported at some centres in Ontario.

There is substantial evidence of suboptimal prescribing of ciprofloxacin in Canada; reports of suboptimal use range from 40% to 60%. Of particular concern to the Subcommittee was evidence based on 1999 IMS data for Ontario that 15% of ciprofloxacin is being prescribed for acute bronchitis; a further 8% for pneumonia. The use of ciprofloxacin for the treatment of acute bronchitis is not supported by clinical practice guidelines. In addition, given the poor activity of ciprofloxacin against *S. pneumoniae*, the Subcommittee felt that both of these were inappropriate uses of this agent. The Subcommittee concluded that ciprofloxacin was a poor choice in settings where *S. pneumoniae* is considered a significant potential pathogen. Similarly, the Subcommittee recommended that ciprofloxacin should not be used for the treatment of skin and soft tissue and other infections where *S. aureus* or Group A streptococcus are considered the predominant pathogens. Furthermore, based on its superior efficacy against *Pseudomonas* compared with other available agents, the Subcommittee felt that, for many indications, ciprofloxacin should only be used when the infection is caused by *Pseudomonas*. It was also noted that the cost of ciprofloxacin is significantly higher than first–line agents.

Levofloxacin: Levofloxacin had been listed in the Formulary as a Limited Use product for the second–line treatment of respiratory infections. However, based on concerns about potentially inappropriate usage as well as increasing resistance, the Limited Use Criteria of levofloxacin have been modified.

General concerns about the emergence of fluoroquinolone resistance have already been mentioned. In addition, there have been several reports of cross-resistance of ciprofloxacin–resistant *S. pneumoniae* isolates to newer fluoroquinolones. It was the opinion of the Subcommittee that the newer generation of fluoroquinolones should be preserved for use against penicillin-resistant *S. pneumoniae* respiratory infections – infections for which there are few effective alternatives. The Subcommittee was also concerned that unrestricted levofloxacin use may displace the macrolides and oral beta–lactam antibiotics.

Based on the available literature, the Subcommittee determined that levofloxacin was as efficacious as, but not superior to, other alternatives for the treatment of community-acquired pneumonia

Rationale for Listing Changes (continued)

and thus, given resistance concerns, should not be used first–line. In the case of urinary tract infections, the Subcommittee noted that equally effective, less expensive quinolones were available. As a result, the Subcommittee recommended that levofloxacin be further restricted to eliminate reimbursement in these indications.

Ofloxacin: Ofloxacin previously had been listed in the Formulary as a General Benefit product. As a multi-source product, ofloxacin is less costly than ciprofloxacin or levofloxacin. Nonetheless, it is expected that widespread use of ofloxacin will lead to resistance levels similar to those observed with other agents in this class. Therefore, as with ciprofloxacin, the ofloxacin listing was changed from a General Benefit to Limited Use in the Formulary. Since ofloxacin has less activity against *Pseudomonas aeruginosa* than ciprofloxacin, the Subcommittee felt that it should be used in place of ciprofloxacin for those indications that do not warrant anti–pseudomonal therapy. Overall, since it offers the best value-for-money in its class, the Limited Use criteria for ofloxacin are generally broader than for the newer quinolones.

Norfloxacin: Norfloxacin had been listed in the Formulary as a General Benefit product. Based on a review of prescribing patterns, the Subcommittee felt that norfloxacin was being used appropriately, mostly for urinary tract infections, and represented the best value–for–money in this class for this indication. Norfloxacin has limited systemic absorption and is used less frequently. Therefore, it was thought that the overuse of norfloxacin was less of a concern than other drugs in this class. Thus, the Subcommittee recommended that norfloxacin continue to be reimbursed as a General Benefit product.

Macrolides

The Antibiotic Subcommittee noted several differences between the quinolone and macrolide antibiotics that warranted comparatively fewer restrictions of the macrolide class. Macrolides are first–line agents for many indications, while quinolones for the most part are not. The use of macrolides has been static, while that of quinolones has been climbing. Furthermore, compared with quinolones, resistance rates to macrolides are not growing as rapidly. And, while quinolones can only be used in adults, macrolides can also be used in both children and adults.

Azithromycin and Clarithromycin: Both azithromycin and clarithromycin are listed in the Formulary as General Benefit products. The Subcommittee noted that the main resistance concerns with these agents relate to respiratory pathogens such as *S. pneumoniae, M. catarrhalis* and *H. influenzae*. In Europe, increasing resistance among group A streptococcus has been documented. While resistance rates to these agents in Canada are currently low, it was felt that increasing resistance among *S. pneumoniae* and *M. catarrhalis* may become a problem in the future and should be carefully monitored. Also, in light of new restrictions for the listing of quinolones, a potential increase in macrolide use may result in increased resistance developing to these agents. It was noted that, for the most part, azithromycin and clarithromycin are currently being used in accordance with approved indications and the Ontario Anti–Infective Guidelines. The Subcommittee recommended that these agents continue to be reimbursed as General Benefit products on a conditional basis. Based on concerns related to the possible shift in macrolide use as well as the high cost of these

Rationale for Listing Changes (continued)

agents relative to other listed alternatives, both azithromycin and clarithromycin should be reviewed again in one year's time.

Penicillins

The penicillins are generally approved for the treatment of infections due to susceptible organisms in a wide variety of clinical settings. The most important pathogens in terms of resistance to penicillins include the respiratory pathogens *S. pneumoniae, M. catarrhalis* and *H. influenzae*. While still low, a significant increase in penicillin-resistant *S. pneumoniae* has been observed; a significant increase in beta–lactamase producing *H. influenzae* has also been noted. It was noted that the penicillins are generally used appropriately and are cost-effective. However, probably due to increasing patterns of resistance as well as the increasing use of quinolones and macrolides, the use of penicillins in Ontario has declined substantially over the last five years.

Amoxicillin/clavulanic acid: Amoxicillin/clavulanic acid is listed in the Formulary as a General Benefit product. The Subcommittee noted that the addition of clavulanic acid to amoxicillin has increased its antimicrobial activity to include beta–lactamase producing strains, including *S. aureus* and *H. influenzae*. However, amoxicillin/clavulanic acid was substantially more expensive than other penicillins. Furthermore, based on 1999 IMS data, it was found that 18% of amoxicillin/clavulanic acid was used to treat pharyngitis. Given that 80–90% of pharyngitis is not of bacterial origin, the utilization of this agent may be suboptimal. In light of the high cost of this agent and concerns about its use, the Subcommittee recommended that amoxicillin/clavulanic acid continue to be listed as a General Benefit on a conditional basis and that the listing be reviewed again in one year's time.

Others

Cephalothin was delisted from the Formulary due to its very short half–life, frequent dosing requirements, and better available alternatives. Because of the limited number of claims made, and available alternatives, nalidixic acid, sulfisoxazole and lincomycin have been delisted. Fusidic acid remains as a limited use product; the criteria for use were revised to include infections caused by coagulase–negative Staphylococci.

Concluding Remarks

The Antibiotic Review, resulting in these Formulary revisions, is only one of the many ways that the DQTC serves the Ministry of Health and Long-Term Care and, by extension, the people of Ontario. The DQTC is committed to ensuring that all product listings in the Ontario Drug Benefit Formulary/Comparative Drug Index are reflective of the best clinical evidence.

References

1. Tenover FC, Hughes JM. WHO scientific working group on monitoring and management of bacterial resistance to antimicrobial agents. www.cdc.gov/ncidod/vol1no1/hughes.htm
2. World Health Organization. World Health Organization Report on Infectious Diseases 2000 – Overcoming Antimicrobial Resistance. www.who.org
3. Tenover FC, Hughes JM. The challenges of emerging infectious diseases. Development and spread of multiply-resistant bacterialpathogens. JAMA 1996;275:300–304.
4. Health Canada www.hc–sc.gc.ca/english/antires.htm
5. Preston M, Borczyk A, Jamieson F. Epidemic methicillin–resistant *Staphylococcus aureus* strain—Ontario. Can Commun Dis Rep (Canada), Mar 15 1998, 24(6):47–9.
6. Simor A, Ofner–Angostini M, Bryce E, et al. MRSA in Canada: Five years of rational surveillance. 40th ICAAC Conference, Toronto. September 17–20, 2000. (Abstract 159)
7. Simor A, Ofner–Agostini M, Paton S, et al. The Canadian Nosocomial Infection Surveillance Program: Results of the first 18 months of surveillance for methicillin-resistant *Staphylococcus aureus* in Canadian hospitals. Can Commun Dis Rep 1997;23:41–45.
8. McGeer A, Low D, Conly J, et al. Methicillin–resistant *Staphylococcus aureus* in Ontario. Can Commun Dis Rep 1997;23:45–46.
9. Conly JM, Ofner ME, Paton S, et al. The emerging epidemiology of vancomycin resistant enterococci in Canada 1993–1998: Results from the Canadian Nosocomial Infection Surveillance Program (CNISP) Passive Reporting Network. Can J Infect Dis 1999;10(Suppl D):38D.
10. Conly JM. Clostridium difficile–associated diarrhea – The new scourge of the health care facility. Can J Infect Dis 2000;11:25–27.
11. Richter SS, Brueggemann AB, Huynh HK, et al. A 1997–1998 national surveillance study: *Moraxella catarrhalis* and *Haemophilus influenzae* antimicrobial resistance in 34 US institutions. Int J Antimicrob Agents 1999;13:99–107.
12. Thornsberry C, Jones ME, Hickey ML, et al. Resistance surveillance of *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* isolated in the United States, 1997–1998. J Antimicrob Chemother 1999;44:749–759.
13. Health Canada and the Canadian Infectious Diseases Society. Controlling antimicrobial resistance: an integrated action plan for Canadians. Can Commun Dis Rep 1997;2357(Suppl):1–32.
14. Canadian Committee on Antibiotic Resistance. www.ccar–ccra.org
15. Do Bugs need Drugs? A community project for the wise use of antibiotics. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco. September 26 – 29, 1999. (Abstract)
16. Stewart J, Pilla J, Dunn L. Pilot Study for appropriate anti-infective community therapy; effect of a guideline – based strategy to optimize use of antibiotics. Can Farm Physician 2000; 46: 851–59.
17. Canadian Committee on Antibiotic Resistance (CCAR). Controlling antimicrobial resistance in Canada – strategies, perspectives, programs. Can J Infect Dis 2000;11(Suppl C):1C–28C.
18. Gould IM. A review of the role of antibiotic policies in the control of antibiotic resistance. J Antimicrob Chemother 1999;43:459–465.
19. Westh H, Jarlov O, Kjersem H, Rosdahl VT. The disappearance of multiresistant *Staphylococcus aureus* in Denmark: changes in strains of the 83A complex between 1969 and 1989. Clin Infect Dis 1992;14:1186–1194.
20. Seppala H, Klaukka T, Vuopio–Varkila J, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in Group A Streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. N Engl J Med 1997;337:441–6.
21. Levine MAH, Pradhan A. Can the health care system buy better antibiotic prescribing behaviour? CMAJ 1999;160:1023–1024.
22. Wang EE, Einarson TR, Kellner JD, Conly JM. Antibiotic prescribing for Canadian preschool children: evidence of overprescribing for viral respiratory infections. Clin Infect Dis 1999;29:155–60.
23. United States Centres for Disease Control and Prevention. www.cdc.gov
24. Ministry of Health, Public Health Branch. Strategic Planning for Antibiotic Resistance in Ontario, Conference, Toronto, March 25, 1997.
25. Chen DK, McGeer A, De Azavedo JC, Low DE. Decreased susceptibility of *Streptococcus pneumoniae* to fluroquinolones in Canada. New Engl J Med 1999; 341:233–9.

Appendix A: Summary of Listing Changes

Summary of Listing Changes – Quinolones		
Drug / Strength	**Average Cost**	**Listing Status**
ciprofloxacin 250mg, 500mg, 750mg tablets, 10g/100mL Oral Susp	$50.12 (500mg bid x 10d)	Limited Use for the treatment of patients with: **SST/BJ (Gram negative bacteria):** Skin/soft tissue & bone/ joint infection due to gram negative bacteria; severe diabetic foot infection; severe otitis externa; decubitus ulcers **GU Tract:** Urinary tract infection / prostatitis / epididymitis caused by *Pseudomonas;* sexually transmitted diseases **COPD with risk:** Acute bacterial exacerbation of chronic obstructive pulmonary disease (COPD) with risk factors[1]; bronchiectasis; pneumonic illness with cystic fibrosis **GI:** Traveller's diarrhea; enteric fever syndromes **Step-Down:** Step-down therapy after parenteral therapy or hospital/ emergency department discharge (e.g. febrile neutropenia) Exceptional cases of allergy or intolerance to all other appropriate therapies.
levofloxacin 250mg, 500mg tablets	$50.10 (500mg od x 10d)	Limited Use for the treatment of patients with: **CAP with co-morbidity:** Community acquired pneumonia with co-morbid illnesses or failure to first-line therapy. **COPD with risk:** Acute bacterial exacerbation of chronic obstructive pulmonary disease (COPD) with risk factors[1]; bronchiectasis. **Step-Down:** Step-down therapy after parenteral therapy or hospital emergency department discharge. Exceptional cases of allergy or intolerance to all other appropriate therapies.
ofloxacin 200mg, 300mg 400mg tablets	$28.98 – 34.05 (200 – 400mg bid x 10d)	Limited Use for the treatment of patients with: **SST/BJ (Gram negative bacteria):** Skin/soft tissue & bone/joint infection due to gram negative bacteria; severe diabetic foot infection. **GU Tract:** Urinary tract infection / prostatitis / epididymitis; sexually transmitted disease. **COPD with risk:** Acute bacterial exacerbation of chronic obstructive pulmonary disease (COPD) with risk factors 1 ; bronchiectasis. **GI:** Traveller's diarrhea; enteric fever syndromes. **Step-Down:** Step-down therapy after parenteral therapy or hospital/ emergency department discharge. Exceptional cases of allergy or intolerance to all other appropriate therapies.
norfloxacin 400mg tablet	$30.51 (400mg bid x 10d)	General Benefit
nalidixic acid 500mg tablet	$21.40 (500mg qid)	Delisted

[1] Risk factors include: poor pulmonary lung function (FEV1 below 50% predicted level), age over 65 years, comorbid medical illness (congestive heart failure, diabetes, chronic renal failure, chronic liver disease), chronic corticosteroid use, malnutrition, prolonged duration of disease, or 4 or more exacerbations per year.

Appendix A: Summary of Listing Changes (continued)

Summary of Listing Changes – Macrolides		
Drug / Strength	**Average Cost**	**Listing Status**
azithromycin 250mg tablet 250mg capsule 100mg/mL O/L 200mg/5mL O/L	$29.60 (500mg x 1d, then 250mg od x 4d) $16.00 (10mg/kg/d x 1d, then 5mg/kg/d od x 4 d, 10kg child)	General Benefit, to be reviewed in one year
clarithromycin 250mg tablet	$29.58 (250mg bid x 10d)	General Benefit, to be reviewed in one year
125mg/5mL Ped Gran	$15.57 (15mg/kg/d x 10d, 10kg child)	
erythromycin	$1.73 – 16.96	General Benefit

Summary of Listing Changes – Penicillins		
Drug / Strength	**Average Cost**	**Listing Status**
amoxicillin, ampicillin, bacampicillin, cloxacillin, penicillin G,penicillin V, pivampicillin, and pivmecillinam	$1.70 – 18.69	General Benefit
amoxicillin/ clavulanic acid	$26.19 – 40.03 (250/125mg to 500/150mg tid x 10d)	General Benefit, to be reviewed in one year

Summary of Listing Changes – Cephalosporins		
Drug / Strength	**Average Cost**	**Listing Status**
cefadroxil, cefixime, cefprozil, cefuroxime axetil, cephalexin, cefazolin, ceftriaxone, and cefaclor	$5.97 – 680.00	General Benefit
cephalothin	$174.59 (1g IV q6h x 10d)	Delisted

Appendix A: Summary of Listing Changes (continued)

Summary of Listing Changes – Others		
Drug / Strength	**Average Cost**	**Listing Status**
gentamicin, tobramycin, neomycin	$170 – 210 (5mg/kg/day x 10d, 70kg pt)	General Benefit
trimethoprim, trimethoprim/sulfa -methoxazole, trimethoprim/sulfadiazine dapsone	$0.68 – 9.90 (10d Tx)	General Benefit
sulfisoxazole	$1.56 – 3.11 (10d Tx)	Delisted
metronidazole	$8 – 36 (10d Tx)	General Benefit
lincomycin	$21 – 28 (10d Tx)	Delisted
clindamycin	$23 – 62 (150–300mgtid/qid, 10d)	General Benefit
tetracycline	$0.76 (250mg qid)	General Benefit
fusidic acid sodium fusidate	$34 (500mg tid, 10d)	Limited Use: As part of combination therapy, for the treatment of serious infections confirmed on culture to be caused by a strain of *S. aureus* or coagulase–negative Staphylococci likely susceptible to fusidic acid where standard anti–staphylococcal agents are precluded because of allergy, resistance or treatment failure.
nitrofurantoin	$9 – 18	General Benefit
iodoquinol	$12 (650mg tid, 10d)	General Benefit

Appendix B: International/National Resistance Programs

Antibiotics have been the foundation of infectious disease therapy since the 1940s. But their healing power is being diminished through their widespread and inappropriate use. Increasingly, bacteria are becoming resistant to antibiotic treatments, requiring more intensive therapies and leading potentially to untreatable illnesses. Jurisdictions across Canada and around the globe are mobilizing efforts to combat the growing threat of antibiotic resistance.

Addressing the judicious use of antibiotics by doctors and patients is a cornerstone of most global strategies. A study on antibiotic prescribing for Canadian preschool children revealed that 51% of the reviewed prescriptions were unnecessary. This experience was similar to one in the U.S., where the Center for Disease Control estimated that 50 percent of all antibiotic prescriptions were not needed.

Ontario is doing its part, with a number of initiatives already underway to address this public health issue. For example, the review of drug products listed on the Ontario Drug Benefit Formulary is consistent with other jurisdictions across Canada and around the world.

The following chart summarizes some of the initiatives underway. It is based on a Communications Analysis on Antimicrobial Resistance[17] sponsored by the Canadian Committee on Antibiotic Resistance (December 2000) and an interprovincial survey of antibiotics (September 1999) conduted by Drug Programs Branch.

Appendix B: International/National Resistance Programs

	Jurisdiction	Organization	Project
Canada	**National**	Population and Public Health Branch, Health Canada	Established advisory group on antimicrobial resistance, which helped to create standards for Canadian laboratories and provides surveillance information on antibiotic resistance.
		Canadian Committee on Antibiotic Resistance www.ccar–ccra.org	Committee of not-for-profit and government agencies that was created to co-ordinate activities and information for health care professionals, patients, the general public and others. The goal is to make Canada an international leader on this issue. Antibiotic Resistance Tool Kit for Physicians: www.ccar–ccra.org/tool_kit–e.htm
		National Information Program on Antibiotics and Antibiotic Awareness Week www.antibiotics–info.org	Privately funded partnership of medical organizations aimed at educating physicians and consumers about the appropriate use of antibiotics through web sites, media campaigns and the launch of Antibiotic Awareness Week.
		Canadian Pediatric Society www.cps.ca	Developed several position papers on the issue and provides educational materials, tool kits and articles for physicians and health care consumers to increase awareness.
	Saskatchewan	Provincial government	Restricted use with criteria for some quinolones, macrolides, and cephalosporins.
	Manitoba	Provincial government	Restricted use with criteria, or pre-approval guidelines for some quinolones, macrolides, and cephalosporins.
	British Columbia	Public/private sector including provincial government	Antibiotic Resistance Education Program: Survey results showed that antibiotic prescription practices changed as a result of resource packages to primary physicians, media campaign, etc.
	Ontario	Provincial government	Multi-disciplinary approach to improve prescribing practices through awareness and regulation. Reviewed listing status of antibiotics on ODB Formulary. In 1997, a steering committee was established to develop strategies to combat resistance.
International	**Global**	World Health Organization www.who.org	Provides international leadership by convening conferences to develop global strategies to deal with the issue. Conducts surveillance of resistance, training courses and research.
		Alliance for the Prudent Use of Antibiotics www.healthsci.tufts.edu/apua/	Non-profit international organization with members in 90 countries. Aims to promote global public health by raising public awareness through education and research projects on proper antibiotic use and antibiotic resistance.
	United States	Centres for Disease Control and Prevention	Developed educational materials on optimal use of antibiotics and a hospital infections program. The CDC relies on behavioral/educational approaches to modifying prescribing practices. Uses web site for data collection.
	Finland *Considered an international model	Joint program of seven organizations	In 1999, launched national current care guidelines for infections. Public and professional education program with a strong emphasis on monitoring changes in treatment and diagnosis, studying physician/ patient attitudes, assessing costs, etc.
	United Kingdom	UK Department of Health www.doh.gov.uk/antibioticresistance/index.htm	Developed clinical prescribing practice guidelines for optimal use of antibiotics and has launched a national publicity and educational campaign and web site.
		Public Health Laboratory Service	Developed antibiotic guidance template of primary care to help clinicians and physicians develop antibiotic guidance.

Ontario

Ministry of Health and
Long-Term Care

DQTC
Drug Quality and Therapeutics Committee

Drug Quality and Therapeutics Committee Bulletin
Antibiotic Review and ODB Formulary Listing Changes

Questions and Answers for Health Practitioners

1. Why was the review undertaken?

- Rising rates of antimicrobial resistance have evolved into a significant public health concern. The morbidity, mortality and financial costs of multiple drug resistant infections for which there are few or no effective therapies pose an increasing burden for health care systems.
- The purpose of this review was to assess the increasing threat of antimicrobial resistance and, as part of a broader strategy, to ensure that all antibiotics listed in the Ontario Drug Benefit Formulary/Comparative Drug Index are being used appropriately in accordance with current clinical evidence.

2. What are the key resistance concerns?

- In Canada, concerns have focused primarily on resistance to common causes of community-acquired infectious diseases and selected hospital-acquired infections.
- The most important strains of resistant bacteria are penicillin-resistant Streptococcus pneumoniae (PRSP), methicillin-resistant Staphylococccus aureus (MRSA), and vancomycin-resistant enterococci (VRE).

3. Was this a cost-containment issue?

- No. While cost-effective drug therapy is one of the priorities of the Ontario Ministry of Health and Long-Term Care, this review was undertaken primarily to address rising concerns about the increasing threat of antimicrobial resistance.

4. What are the key changes? Why?

- Ciprofloxacin, levofloxacin and ofloxacin will now be listed as Limited Use products; nor-floxacin will remain a General Benefit because the review showed that the product is generally being used appropriately. There was particular concern about increasing rates of resistance to
- the quinolones and the spread of cross-resistance from older to newer quinolones.
- Three agents - clarithromycin, azithromycin and amoxicillin/clavulanic acid will remain as General Benefit products on a conditional basis; their respective usage and resistance patterns will be reassessed in one year's time.

5. Why are you making it harder for me to prescribe some specific antibiotics?

- The listings for ciprofloxacin, levofloxacin and ofloxacin have been revised in order to ensure the most appropriate use of these agents and to limit the spread of resistance.
- The Limited Use Criteria outlined for each of the fluoroquinolones are in keeping with current clinical evidence.

6. The Limited Use system is a burden. Why doesn't the Ministry simplify it?

- As part of the Ministry's ongoing process to simplify the Limited Use process, a new Limited Use prescription form was introduced on July 1, 1999. The new prescription form has been stream-lined and simplified to make it easier to complete.
- A Limited Use tripartite committee of the Ontario Medical Association, the Ontario Pharmacists' Association and the Ministry of Health and Long-Term Care meets regularly to discuss ways to improve the Limited Use process.
- A drug utilisation review on the use of anti-infectives has been commissioned by the ministry. This will assist in determining future courses of action.

7. Do you have any tips for discussing the role of antibiotics with my patients?

- Yes, the Ministry has created a pamphlet for patients explaining the role of antibiotics and antibiotic resistance.
- Prescription pads are available explaining why antibiotics have not been prescribed. For example, the Canadian Committee on Antibiotic Resistance (CCAR) and The Canadian Infectious Disease Society (CIDS) have produced a template that is available on the internet at : www.infectnet.com/Contents/Antibiotics/Ant_Links_Pro/ant_links_pro.htm
- Other patient information is available on the CCAR web site : www.ccar-ccra.org.

8. What impact can I, as an individual doctor, have?

- Every physician has a part to play to ensure that antibiotics are used judiciously with a goal tolimiting the spread of antimicrobial resistance.
- Since general practitioners prescribe approximately 75% of all antibiotics in Canada, the combined effect of each physician acting locally can have a significant impact on this important provincial, national and global public health problem.

9. What are other provinces and jurisdictions doing?

- Other provinces (e.g. Saskatchewan, Manitoba, Nova Scotia and Prince Edward Island) have also restricted the use of the quinolone antibiotics for similar reasons as those given by the Ministry of Health and Long-Term Care.
- A number of national and international programs have been established around the world to track antibiotic usage and antimicrobial resistance, and to disseminate educational materials. Please see Appendix B of the attached DQTC Bulletin for more details.

10. Is any action being taken on the use of antibiotics in veterinary medicine?

- Health Canada and individual provinces, including Ontario, have initiated a number of activities to address this area of concern. Information about what is being done in Ontario can be found at the following web site : www.gov.on.ca/OMAFRA

© 2000 Queen's Printer for Ontario | Last Modified: 02/13/2001 16:19:02